



Surface modification of cardiovascular materials and implants



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ABSTRACT

Cardiovascular implants find wide clinical applications, making a great contribution to the treatment of cardiovascular diseases. Such devices, endovascular stents, artificial vascular grafts, prosthetic heart valves to name a few typical examples, have been the mainstay of cardiovascular surgery. However, failure cases of the implants still exist, which urge us to understand what has happened at the blood-contacting interface and how the tissues have responded during the post-implantation period. Aiming to eliminate these pathological events, various approaches of surface modification of the cardiovascular devices have been used in order to improve hemocompatibility and cytocompatibility. In this review, the blood–biomaterial interfacial events and the evolution of the surface modification strategies are discussed, together with the recent developments on the surface modification of cardiovascular materials like biomimetic extracellular matrix and accelerated endothelialization. These novel surface modification strategies open a new chapter on designing ideal blood-friendly implantable materials.

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1. Introduction

Cardiovascular diseases (CVDs) are the leading causes of premature death globally and bring tremendous financial burden in every country [1]. The conservative medical treatment is not effective enough for critically ill patients. However, the developments in the field of blood-contacting materials make it possible to apply interventional surgery and implantable devices in clinics for saving the life of these patients. Although various commercial cardiovascular implants are approved by FDA and millions of patients benefit from these products, unfortunately, there still does not exist an ideal device which can help patients recover completely and avoid the risks of CVDs [2].

Taking endovascular stents as a first example, the intervention process as such induces an inflammatory reaction. The limited hemocompatibility of the surface and the release of toxic ions such as Cr, Ni, Co from a bare metal stent (BMS) result in restenosis, which is a main reason of death in patients with percutaneous transluminal coronary angioplasty (PTCA) [3]. Drug eluting stent (DES) as the subsequently developed device was considered as the breakthrough in stent design. They, however, performed not so well in long-term clinical studies [4]. It is confirmed that the released drug from the stent surface delays endothelialization and triggers late thrombosis [5]. Acting as the similar function with stents, vascular grafts are also used in case of

occluded coronary arteries by the methods of replacing or bypassing the diseased arteries. The surface of artificial grafts with poor biocompatibility induces the restenosis and thrombosis, especially the grafts with an inner diameter smaller than 5 mm. In this regard, there is a clinical need for mechanically favorable, biocompatible small-diameter bypass grafts that prevent thrombosis and intimal hyperplasia [6], both of which are the fatal risks occurring after the implantation of endovascular stents and synthetic vascular grafts.

Another typical example of cardiovascular implants is the ventricular assist device (VAD), which supports blood circulation as a blood pump. Although there are no issues of endothelial cell damage and intimal hyperplasia, the interaction between blood and the foreign material generates common complications like thromboembolism and poses the risk of infection [7]. Therefore, it is a major challenge to design and prepare biomaterials with excellent hemocompatibility in order to create a safe blood-contacting surface balancing thrombus formation and active antithrombogenic effects [8]. Besides vascular stents, synthetic grafts and VAD, artificial heart valves (AHVs) are also the most widely used cardiovascular devices. Valvular heart disease is classified into two types: congenital and acquired. Respectively, bioprosthetic heart valves (BHV) and mechanical heart valve (MHV) are employed [9]. However, the patients have to be faced with calcification of AHVs and abrasion at the surface of BHV, thrombosis on surface of MHV and the hidden danger of taking immuno-suppressive or anti-coagulant therapy drug whole life [10]. The similar situation also occurs to other cardiovascular devices, such as circulatory support devices, hemodialysis, blood oxygenators, other interventional catheters and extracorporeal tubings.

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According to the different functions and requirements for various devices, the materials applied clinically are divided into three categories: metals and alloys (e.g. 316L stainless steel in stents, Nitinol in self-expanding carotid stent, or Ti alloy in AHV), ceramics (e.g. SiC, DLC in artificial heart valves), and polymers (e.g. ePTFE or PET in vascular grafts, PU in artificial heart valves). None of these cardiovascular materials—metals or alloys, ceramics or polymers, presents both excellent hemocompatibility and tissue compatibility satisfying current clinic requirements [11]. In order to overcome unexpected interaction between surface and tissue, surface modification has been introduced for cardiovascular devices to allow independent tailoring of surface and bulk properties [12,13].

2. Blood–biomaterial interfacial events and interaction mechanism

Most problems of cardiovascular devices happen at the non-suitable blood–material interface, which is the initial factor for the implant failure [14]. Integration of materials or devices in cardiovascular system leads to a number of unfavorable reactions: 1) protein adsorption on the materials and changes of conformation resulting in the loss of their biological function, 2) initiation of coagulation cascade and the formation of fibrin, 3) activation of the complement cascade as part of the innate immune system and local inflammation, and 4) for implants like stents and synthetic grafts, dysfunction of the endothelium caused by the damage of endothelial cells (ECs) and hyperplasia of smooth muscle cells (SMCs).

The coagulation cascade is considered as a complex physiological response system, with potent feedback and feedforward loops as shown in Fig. 1. It is generally accepted that plasma and plasma proteins are the most significant components of blood [15]. Once a foreign material is exposed to blood, plasma proteins adsorb on the surface within few minutes [16]. The surface physical or chemical surface characteristics urge the transformation of the adsorbed proteins and then the exposure of active site. These conformation changes lead to the activation of coagulation factor XII and activate the intrinsic pathway [17,18]. Afterwards, blood platelets respond to many external stimuli, such as thrombin from the coagulation cascade, adenosine diphosphate released from destroyed cells, and shear force. They adhere to mechanically deformed

von Willebrand factor on activated endothelium and sub-endothelium, or to denatured fibrinogen of fibrin [19]. These events lead to the adhesion, activation and aggregation of platelets at any thrombogenic surface such as the injured endothelium when a stent is inserted and expanded or at the artificial surfaces of synthetic vascular grafts. Platelet activation leads to device failure by the formation of a stable thrombus, an occlusive and lumen narrowing complex with fibrin incorporated in the growing platelets plug [20]. Therefore the evaluation of platelet activation and fibrinogen deformation is a key approach in the evaluation of the hemocompatibility of a designed or modified material.

Besides the activation of platelets and fibrinogen deformation, thrombin activation is a key step in common coagulation pathway and in feedback loops. It acts as a protease that converts soluble fibrinogen into fibrin, which polymerizes to insoluble clots. Thrombin also catalyzes other coagulation related reactions, such as amplifying the FXIa conversion from FXI in the extrinsic system [21]. Now much attention has been paid to control the behavior of thrombin. Direct thrombin inhibitors, widely used pharmaceutically, present a high potential application value in anti-coagulant surface modification [22]. While protein adsorption to the surface occurs within seconds of blood–bio-material contact, the activation of the clotting cascade to thrombin and fibrin formation takes 10 to 15 minutes, followed by the activation of platelets shortly thereafter. The complement activation and associated inflammatory reactions occur in parallel, playing the dominant role in body's defense mechanisms against foreign materials [23]. Therefore regulation of complement pathway in order to control coagulation system is also a fascinating method to obtain new generation blood-contacting surface with excellent hemocompatibility.

3. Surface modification for improving hemocompatibility

In the past few decades, much research has been done to improve the surface properties of blood-contacting artificial devices. Nowadays, 316L SS or Co-Cr based vascular stents (e.g. BiodivYsio™ AS and Multi-link Vision™), low temperature isotropic pyrolytic carbon based artificial heart valves (Edward-Duromedics bileaflet valve heart valve), expanded polytetrafluoroethylene (ePTFE) or polyethylene terephthalate (PET) based vascular grafts (Dacron®) have found clinical application. While

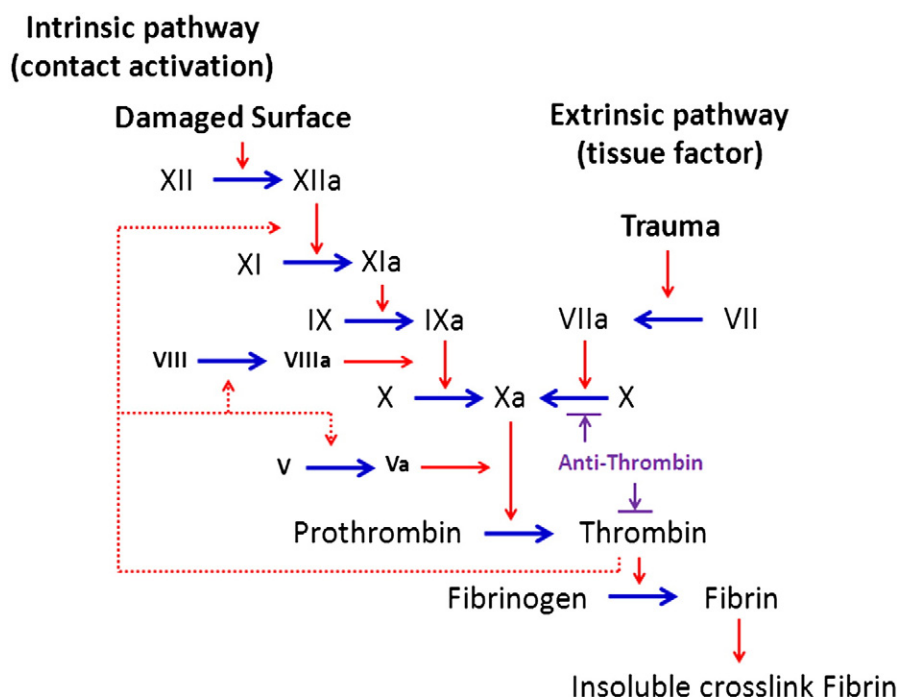


Fig. 1. Extrinsic and intrinsic pathways of coagulation cascade.

the clinical studies have confirmed the release of toxic ion from metals or alloys and the degradation of implanted polymers cause a series of inflammatory reactions, such as restenosis and calcification [24]. Various strategies of surface modification for cardiovascular materials have been developed during the recent 30 years. Typical examples are the applications of DLC films and heparin coatings on the substrate. Through effort of a few generations, the surface modification techniques have made great progress and the modification strategies developed from the concept of bio-inertness to bio-activity, and now they apply biomimetic strategies and the in-situ induced endothelialization, just as shown in Fig. 2.

3.1. Bio-inert coatings

The first generation strategy of surface modification has been the bioinert coating. It was believed that coverage of a bulk material, serving as a barrier, may decrease the complication rate if the interaction between the material and biological system is reduced. Based on this hypothesis, numerous meaningful attempts have been made by different research groups.

3.1.1. Inorganic coating

Inorganic coating has been already widely used for the surface modification of cardiovascular devices, such as DLC on AHVs [25], DLC and TiN coating in VADs [7], and Ti–O film on stents [26]. Before the preparation on commercial products, various coatings have been tested. Gold, well-known as a kind of inert metal, was used at early stages as a protecting coating on stainless steel stents, inspired by the dental application. What is more, its good radiopacity was a motivation to apply it onto stents [27]. But the six-month follow-up clinical results were not satisfactory. Neointimal proliferation and restenosis still existed among the patients. The long-term mortality risks also increased compared with the uncoated stents [28]. Another two meaningful jobs were the involvement of bioinert ceramics SiC and DLC coating. It has been demonstrated that SiC resists the adhesion of platelets and decreases inflammatory reactions [29]. Compared with SiC, DLC coating has similar advantages, including higher hardness and smoothness, lower frictional coefficient, chemical inertness and biostability. Especially, the good hemocompatibility of DLC makes it suitable for the applications on vascular stents, AHVs and VADs [30]. Besides, due to their outstanding biocompatibility, titanium and its alloys also found application in various biomedical devices in dental or orthopedic surgery. The excellent properties such as good chemical inertness, corrosion resistance, and biocompatibility are attributed to the surface oxide layer [31]. Though pure Ti has limited application as bulk material in stents or AHVs, NiTi shape memory alloy and Ti-based ultrathin films are widely applied in cardiovascular devices, like coronary and carotid stents and AHVs. The designs of Ti–O [26], Ti–N [32], Ti–N–O [33,34], or their complex film [35] coatings for surface treatment based on the

noted properties were achieved by various film-preparing techniques, among which magnetron sputtering, filtered cathodic vacuum arc deposition and plasma immersion ion implantation and deposition are the most successful ones. The equipment of the vacuum devices and related principles were elaborated in some other plasma surface modification reviews [36].

3.1.2. Organic coating

Besides bioinert metal-oxide films and biocompatible ceramic coatings, polymer modified substrates have been prepared by diverse techniques [37]. Polymer brush is an interesting model which is widely applied as a bioinert or bioactive modification film in biofouling system. Polyethylene oxide (PEO) and the related molecule polyethylene glycol (PEG) with hydrophilic long chain ($\text{HO} - [\text{CH}_2 - \text{CH}_2 - \text{O}]_n - \text{H}$) are well-known to display excellent anti-adhesion ability [38]. The PEG modified surface presents excellent hemocompatibility, for adhesion resistance to small biomolecules and cells such as fibrinogen, platelets and leukocytes [39]. Although, success of these attempts has been reported in some laboratory studies, in vivo and clinical outcomes are disappointing by low resistance of PEG coatings. So their use in the surface modification of cardiovascular materials is limited [40]. Another method to prepare anti-fouling polymer coating is the use of zwitterion, typically those which contain phosphorylcholine, carboxybetaine and sulfobetaine, the structures of which are shown in Fig. 3. 2-methacryloyloxyethyl phosphorylcholine (MPC) polymer, which was developed two decades ago for its good blood compatibility [41], is a phospholipid polymer acting as a surface component of biomembrane. MPC modified surface could minimize the adsorption of plasma protein, suppress platelet activation and control the coagulation cascade and immune-response effectively. Due to its good blood compatibility, MPC polymer has been used to prepare nonthrombogenic surface, adopted in cardiovascular devices like dialysis, heart pumps or VADs [42]. Currently, scientists begin to graft MPC onto the substrate as an intermediate layer for covalent immobilization of biomolecules like growth factors and antibodies or apply MPC coating as a drug delivery system to prepare bioactive surface [43]. Carboxybetaine and sulfobetaine are also promising candidates for the preparation of anti-fouling surfaces because of their high hydration capacity and electroneutrality. Their high plasma protein adsorption resistance and multiple function groups provide an outstanding platform for the construction of hemocompatibility surface and immobilization of biomolecules [44,45]. However, taking mechanical properties into account, these polymer coatings are not as strong or stable as the DLC or Ti–O film. Therefore, polymer anti-coagulant coatings alone seems not to be an ideal for long term implant but a good choice for short term application, considering their protein resistance initially.

Through physical and chemical surface treatment, blood compatible surfaces are obtained. However the modified material is still a foreign matter to the body. Thus autologous protein and small molecules are introduced to form similar bioinert surfaces [12]. The components of

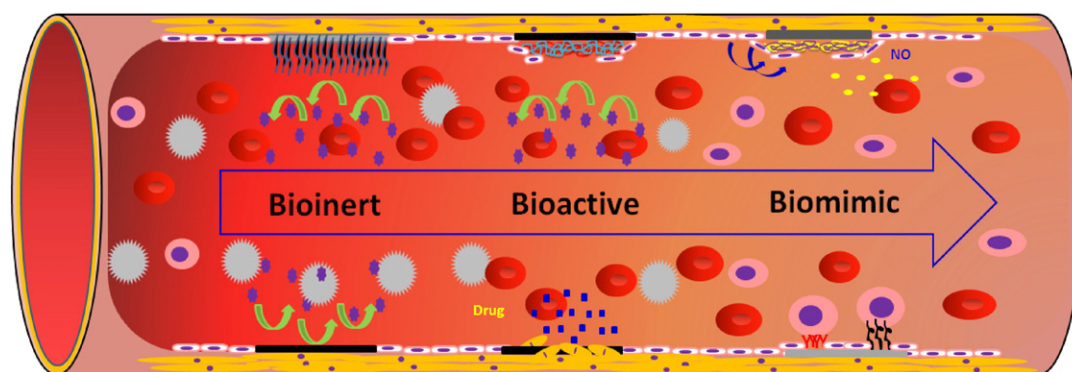


Fig. 2. Evolution of strategies for surface modification in cardiovascular materials.

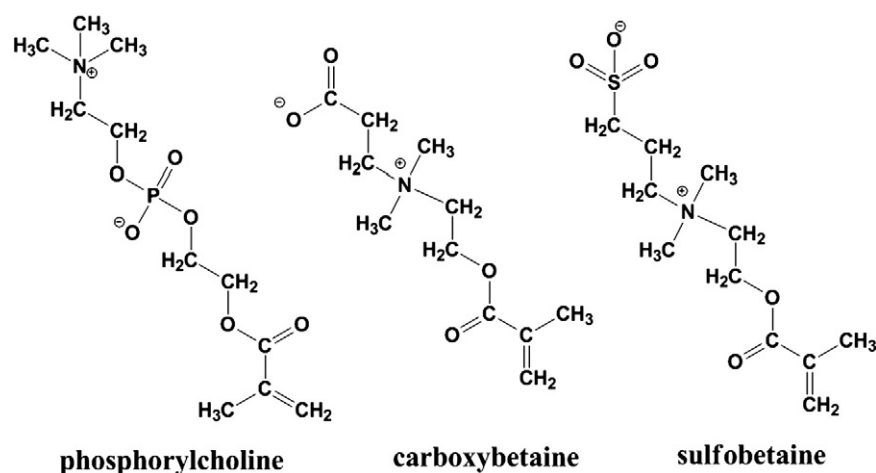


Fig. 3. Molecular structure of phosphorylcholine, carboxybetaine and sulfobetaine.

blood could recognize as friendly landing zone in order to response correctly. Albumin, the most abundant protein in human serum, was first immobilized on polyethylene (PE) as a modified coating by Y Ishikawa in 1986 [46]. Aggregated platelets were observed on the control PE film but not observed on the albumin immobilized PE. This phenomenon also provides some inspiration for further investigation of relationship between surface charge [17,47], functional groups and coagulation. For example, influence in hemocompatibility of reversibly albuminized surfaces with long chained fatty acids and sulfonic acid content in the polymer has been studied [48,49].

With further research, a growing number of scientists pay much more attention to the interaction between different films and blood components. The reason for the superior hemocompatibility of SiC or Ti–O film is discussed by the semi-conductive structure and relative electron transformation from the protecting film to the target proteins in coagulant cascade. For example the interactions between fibrinogen and the coating cause the deposition of fibrin and platelets and ultimately the formation of a thrombus. In some degree, both “bioinert” coatings present bioactive property under the condition of an appropriate conductivity [50,51]. These fascinating results encourage scientists to change the modification strategies from the traditional bioinert coatings to the construction of bioactive coatings.

3.2. Bio-active coatings

Generally speaking, none of any materials could be considered as bioinert. The structures and the properties determine the reaction when applied as a blood-contacting material. Gradually, scientists and engineers tend to adopt the design strategy of bio-active surface modification. According to the rationale of bioactive modification, proteins, drugs and natural and synthetic biomaterials, have been introduced in surface modification for cardiovascular implants or materials and become part of the devices [52]. The typical example is the well-known heparin-coated vascular graft or stent and the second-generation stent–drug eluting stent. The strategy of bioactive coating is the immobilization of pharmacologically active agents that regulate coagulation, complement system and further inflammation responses such as polysaccharides (heparin and hyaluronic acid), anti-coagulant polypeptides (hirudin and related direct thrombin inhibitors), anti-proliferative agents (paclitaxel and sirolimus), functional protein (extracellular matrix proteins, growth factors and antibodies) and nitric oxide releasing compounds. Among all these concepts, heparin bioactive coating is the most widely used in both vascular grafts and stents and clinically the most successfully applied. The functional protein assembly is the typically biomimetic modification strategy

simulating the endothelial cell microenvironment. It will be summarized in detail in the next part of this paper.

3.2.1. Coating of anticoagulant molecule

Heparin, an anticoagulant drug discovered in 1961, is well known as a biologically important polysaccharide. It was later found that the interaction between heparin and antithrombin accelerated their reaction with thrombin, thus avoided the amplification of anticoagulant cascade [53]. Many immobilization strategies have been applied to immobilize heparin onto the metal or polymer cardiovascular materials such as 316L SS, ePTFE, PET, polyurethanes, poly(lactic acid), polypyrrole and polysulfone [54]. And the coating techniques range from the simple physical adsorption to covalent side-on or end-on immobilization. Recent studies have also discovered that heparin, as a linear, unbranched, highly sulfated polysaccharide, presents specific sequences or motifs to reinforce the binding with various proteins, thus contributes to the release of small molecules or functional proteins [55]. In addition, the different concentration of heparin on the surface has different effect on the blood and vascular cells, including endothelial cells (ECs) [56] and smooth muscle cells (SMCs) [57]. Although the pure heparin coating techniques get matured, new designs and methods of using heparin are of great interest to lots of biomedical engineers. David E. Robinson et al. [58] report a method to provide surface gradient of unmodified heparin to study the interaction between heparin and biomolecules and the migration of leukocytes and associated inflammation. Zhilu Yang et al. [59,60] prepare heparin functionalized surface through plasma polymerization on 316L SS stent by covalent immobilization and physical adsorption. The results show that the modified surface improves the hemocompatibility significantly and promotes in vivo re-endothelialization. Ryan A. Hoshi et al. [61] also evaluate the cell behavior on heparin-modified ePTFE vascular grafts. The heparinized surface can modulate the expression of endothelial cell-specific phenotype markers and the phenotype of SMC. As a biomolecule with high degree of carboxylation and sulphonation, heparin forms a polyanion at physiological conditions. Thus, with the incorporation of a biofunctional polycation, layer by layer technique is easy to be realized by alternative immersion. Based on the anti-coagulant heparinized surface, we obtain multifunctional surfaces with antibacterial [62] or endothelialization promoting properties by assembly of chitosan or fibronectin for example [63,64]. These approaches all present promising applications in blood contacting devices.

With the similar function as heparin, direct thrombin inhibitors are a kind of anticoagulant molecules. In contrast to heparin, direct thrombin inhibitors block directly the thrombin active site and consequently inhibit the activity of soluble thrombin. While heparin has no

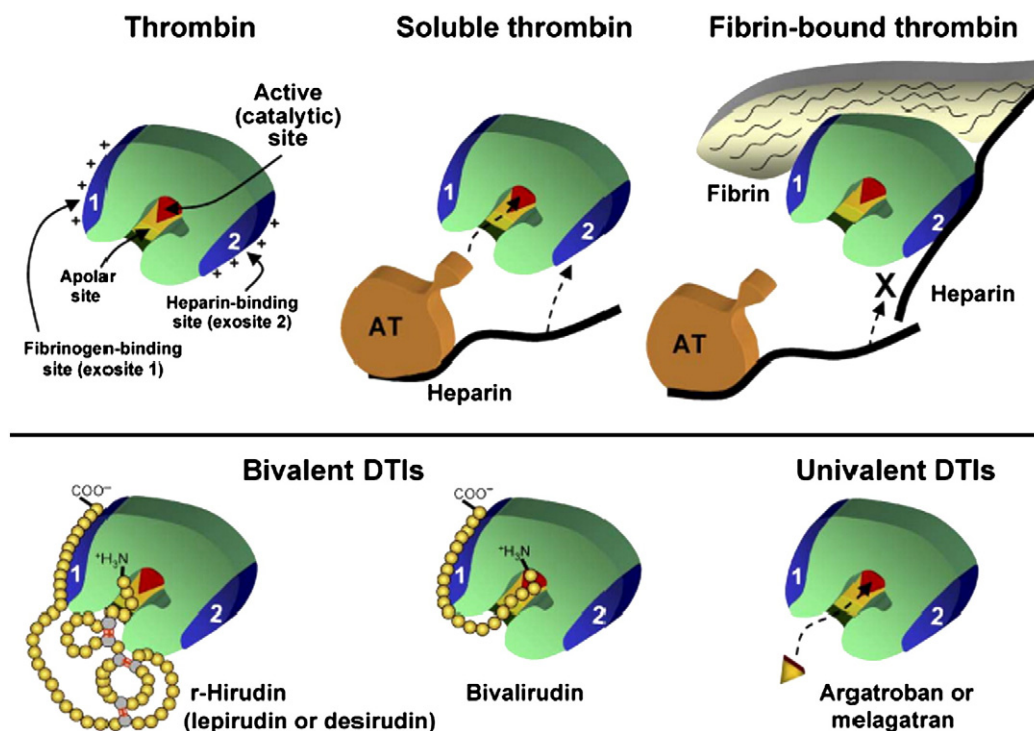


Fig. 4. Schematic representation of thrombin and its inhibition.

activity to inhibit fibrin-bound thrombin, the direct inhibitors can do, as clearly shown in Fig. 4 [65]. Natural direct thrombin inhibitors are hirudin from leech, venoms of some snakes and peptides in salivary glands of some insects [66]. A number of recombinant derivatives of hirudin like lepirudin and desirudin function as thrombin inhibitors as well [67]. Matthew D. Phaneuf et al. [68] systematically study the immobilization of recombinant hirudin on vascular grafts, creating a novel antithrombin surface. Certain disadvantages of hirudin like bleeding, short half-time and immunogenicity limit its application [69]. In contrast, the development of hirudin analog, bivalirudin, exhibits a shorter half-life, predominant non-renal (enzymatic) metabolism, and low immunogenicity. It was first applied onto metallic vascular stent by dopamine and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide (EDC) mediated covalent immobilization relatively in our group. The hemocompatibility of 316L SS surface was improved markedly in vitro and vivo. Furthermore, the attachment, proliferation, migration and function of ECs are promoted notably as well [70,71]. Another direct thrombin inhibitor boophilin, oriented from the cattle tick *Rhipicephalus microplus*, was also immobilized onto Au surface by biotin–neutravidin system, suggesting that the boophilin-coated surfaces will have the advantage of inactivating the initial thrombin formation [72]. Also completely synthetic thrombin inhibitors like D-Phe-Pro-Arg-chloromethylketone [73] and an amidine derivative [74] have been immobilized to surface with good anticoagulant and anti-inflammatory effect. Immobilization processes described above were used as a proof of concept to demonstrate that direct thrombin inhibitors can be immobilized on a surface, maintaining their capacity to bind to and inactivate thrombin. Not only an anti-thrombogenic surface model at present, it shows the potential applications in the surface modification of cardiovascular devices.

The coagulation cascade can be controlled through the involvement of heparin and direct thrombin inhibitors to some extent. Other concepts involve the immobilization of other anticoagulant molecules like thrombomodulin (TM) and nitric oxide (NO) as well. As far back as 1992, TM was first immobilized by Mitsuru Akashi on foreign surface,

and anticoagulant activity was evaluated [75]. Hereafter, TM mobilized surface for improving hemocompatibility has been designed by many other research groups [76]. Up to this time, co-immobilizations of TM/urokinase and TM/endothelial protein C receptor are focused on systematic evaluation of the surfaces prepared in the context of blood–biomaterial interactions [77,78]. NO could modulate blood vessel tone, vascular permeability and inhibit the leucocyte adhesion, platelet activation and SMC hyperplasia [79]. Michele C. Jen et al. [80] and Yajun Weng et al. [81] separately reported the construction of NO releasing system on the substrate of polymer and metal. Both results presented promising application in indwelling cardiovascular devices. While the releasing of NO through polymer reservoir or catalytic generation of NO in-situ by immobilization of NO donors is yet to receive enough clinic tests. A more systematic evaluation of polymer or metal based NO releasing materials will be carried out later. A variety of cascading reactions occur including the intrinsic coagulation pathway, fibrinolysis, complement activation, and inflammation reactions, when blood contacts with foreign surface. More trials on the controlling inflammatory system or complement system by immobilizing key molecules like apyrase [82], CD47 [83], and soluble complement receptor 1 [84] are under investigations, also revealing the widely application prospects.

3.2.2. Drug involved coating

Anticoagulant or antiplatelet and anti-inflammatory agents are widely used in cardiovascular surgery. It is a long history that people takes medicine to cure CVDs such as aspirin, warfarin and clopidogrel. Most people must receive oral anticoagulant drugs after implantation of a stent or the synthetic graft [85]. What deserves to be mentioned is the combination of drugs or agents on medical devices, drug eluting stent, a revolutionary product, has been just brought up in the 1990s. This kind of stent suppresses lumen restenosis by the release of paclitaxel and sirolimus, both of which are anti-proliferative drugs used in the treatment of cancer. They inhibit the cell cycle at different positions, thus the proliferation and growth of SMCs are inhibited

and ultimately SMC death is induced [86]. Unfortunately, adverse effects of delayed re-endothelialization occur, which lead to long-term exposure of the nude stent surface and late stent thrombosis. What is worse, the polymer carrier of the DES induces remarkable inflammation. The current strategies of optimizing DES are preparing new coatings, new platforms and new techniques of elution [87], among which polymer-free DES (porous platforms made by Al_2O_3 , HA, 316L SS etc.) and biodegradable polymer-based DES (PLLA, polycarbonate) are paid more attention compared with the development of new drugs [3,24]. It is also worth mentioning that “gene eluting” has come from concept to reality, benefiting from the rapid development of biotechnology. Vascular gene therapy requires the combination of therapeutic gene product, an appropriate vector and a delivery system for targeted therapy. Among these three parts of gene therapy system, vector system plays the most significant role in treating cardiovascular disease including restenosis, thrombosis, vascular graft disease and chronic vascular occlusion [88]. Plasmids, retroviruses, adenoviruses, and adeno-associated viruses are the four kinds of common vectors. Adenovirus-mediated delivery of endothelial nitric oxide synthase to the blood vessel wall [89] and co-eluting of VEGF plasmid and paclitaxel [90] respectively present the huge potential application of accelerating re-endothelialization and prevention of restenosis. Nowadays, various innovative DES have been undergoing animal experiment and clinical evaluation and the outcome of the studies is highly expected.

3.2.3. Cell-seeding coating

Another effective method to prepare anti-coagulant surface, seeding cells, has been attempted widely. The types of cells are typically blood derived cells ranging from endothelial cells [91,92], endothelial progenitor cells [93,94] to stem cells [95,96]. These surface modification strategies, imitating tissue engineering, are widely applied on synthetic grafts, vascular stents and artificial valves. However, the cell seeding modification requires the harvesting of autologous cells, making these approaches time and cost consuming. Further, the possibility of infection or contamination limits the clinical application.

Actually, bioinert or bioactive coatings are based on the regulation of physical, chemical, or biological properties of the material surface [97]. According to the principle of different techniques for cardiovascular material surface modification, two general categories could be summarized here. 1) physical methods such as spraying, physical vapor deposition, plasma ion immersion and implantation, plasma polymerization and 2) chemical methods such as acid/alkaline treatment, anodic oxidation, silanization etc. Nevertheless, it is difficult to prepare an ideal surface with anticoagulant properties, endothelialization promotion, and SMC inhibition through one or two simple methods. At present, anti-thrombogenic surfaces have been successfully prepared by heparin coating or coupling other anti-biofouling molecules, and widely utilized in blood contacting devices without vessel damage. However, the only anticoagulant property is not enough in some cardiovascular devices like small diameter vascular grafts and endovascular stents [98]. Also, anticoagulant molecules will suffer enzymatic degradation and most polymer coatings are subject to hydrolytic degradation. Preparing durable coating always puzzles biomedical engineers. The damage of ECs and hyperplasia of SMCs cannot be effectively avoided by any purely anticoagulant coating. With deeper understanding of the EC microenvironment, novel healing strategies have been adopted, based on in vivo endothelialization.

4. Biomimetic endothelialization promoted surface modification

The concept of biomimetics is “the study of the formation, structure, or function of biologically produced substances and materials and biological mechanisms and processes, especially for the purpose of synthesizing similar products by artificial mechanisms which mimic natural ones [99].” With respect to surface modification of

cardiovascular materials, these advanced strategies could be classified into three categories.

- (1) Bio-inspired materials or properties used as coating or film to construct blood-contacting surfaces with multiple functions of anti-coagulation and promoted endothelialization.
- (2) Surface of natural endothelium, supported by immobilization of biomolecules and construction of an EC-friendly microenvironment.
- (3) Rapid endothelialization by mimicking a self-healing system with accelerated repair of the damaged endothelium human by supporting the homing of stem cells or progenitor cells to the site of the injury.

4.1. Bio-inspired material in cardiovascular surface modification

Learning from nature is always the source of creative ideas. The selection of a unique material or property discovered in biology or nature could serve as bio-inspiration [100]. These bio-inspired, smart materials are attracting more and more interest. Creative jobs and related systematic evaluations have been done to provide the possibility for pre-clinic application. In 2007, Haeshin Lee et al. [101] reported a simple and versatile strategy for surface modification of multiple classes of materials inspired by the behavior of mussels. Previous work has demonstrated that the key molecule in mussel adhesive protein is dopamine and its catechol groups. The polydopamine (PDA) coating not only shows a high strength to various substrates but also exploits an extremely potential platform for secondary reactions [102,103]. Since then, PDA assisted grafting or co-immobilization of diverse biomolecules is adopted in different fields, including surface modification of vascular stents or grafts, even in vascular tissue engineering (Fig. 5). Zhilu Yang et al. [104] evaluated the potential of PDA coating applied in vascular devices. The results revealed that the PDA coating shows good resistance to the deformation behavior of compression and expansion of a stent. Besides, the hemocompatibility and physiological function of endothelial cells were enhanced compared with the control. Similar evaluations also have been done on mussel-inspired electrospun nanofiber scaffold for vascular tissue engineering [105]. Actually, the substrate ranges from traditional metal to various polymers like ePTFE, PE, PCL, and PU, demonstrating that mussel-inspired PDA layer is a promising and effective strategy for surface modification to realize endothelialization of cardiovascular devices. What's more, PDA layer contributes to secondary surface mediated reactions under oxidizing conditions as a result of its primary amine and catechol end groups [106]. Thus dopamine mediated biomolecule immobilization provides a versatile platform for preparing multifunctional coatings through two methods: 1) synthesis of a biomolecule-dopamine conjugate (heparin for example [107]) and subsequent assembly by the catechol groups and 2) Michael addition or Schiff base reactions between catechol groups with biomolecules carrying amine or thiols (Vascular endothelial growth factor for example [108]). Recently Yu Bin Lee et al. report the dopamine mediated immobilization of the RGD peptide and bFGF on poly(L-lactic acid)-co-poly(ϵ -caprolactone) film. RGD mediated promotion of cell migration and bFGF mediated expression of endothelialization markers demonstrated the synergistic effects on vascular graft materials [109].

Another interesting and important inspiration obtained from nature is the correlation between multi-scale structure and properties. Developing a synthetic liquid-repellent surfaces is currently inspired by the famous “lotus effect” [110] and newly reported approach inspired by Nepenthes pitcher plants [111]. Both strategies emphasize the influence of substrate texture on wettability and cell adhesion. That is the surface at micro/nano-scales could modulate the wettability and affect the attachment and adhesion of blood components, mainly platelets and plasma proteins. Li Chen et al. [112] yielded a surface showing typical nano-scale topography and significantly reducing activation

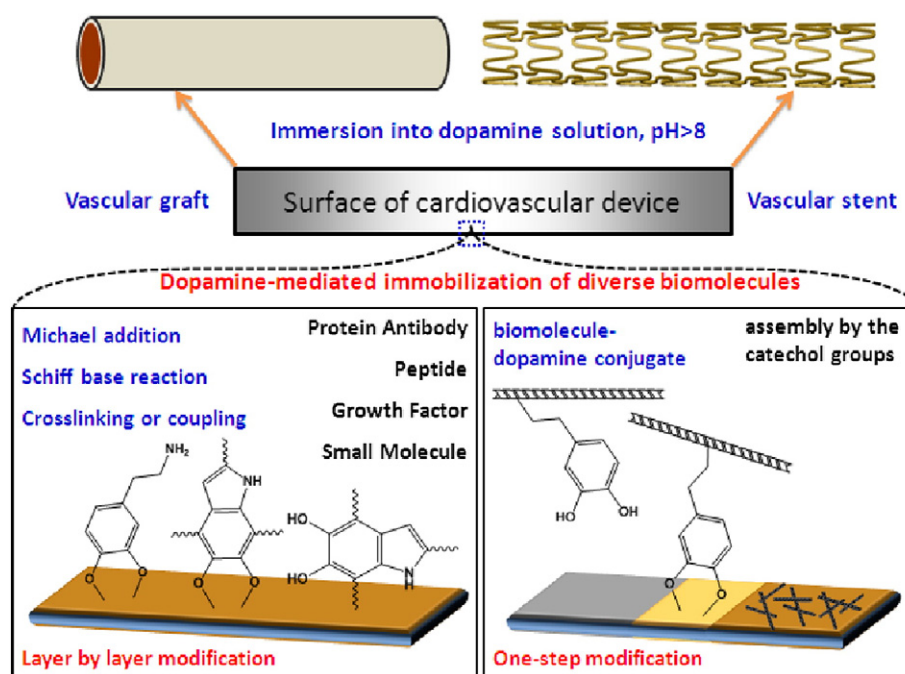


Fig. 5. Dopamine coating applied in surface modification of cardiovascular device.

and adhesion of platelets on silicon nanowire array. Lily Peng et al. [113] investigated the effects of nano-tubular titanium oxide surface on vascular cells. Interestingly, nano-topographical features of titanium nanotubes can be used to promote proliferation and function in ECs and help SMCs maintain their differentiated and non-proliferative phenotype. To mimic the natural blood vessel wall, Honglei Fan et al. [114] built a polydimethylsiloxane model surface consisting of interlaced submicron-ridges and nano-protuberances by simply combining self-assembly, soft lithography and physical treatment. This multi-scale structure remodels the boundary condition of blood, leading to a low collision frequency of platelets and highly optimizing blood compatibility. According to the research, the mentioned micro/nano-topography is considered as patterned surface. The shape and the dimension vary from gratings, pits, posts, islands, and random structures, each of which conducts unique function to ECs, SMCs and fibroblast cells. Feroze Nazneen et al. [115] systematically reviewed the vascular cell responses to micro/nano-structured surfaces. Most results indicate that the patterned surface regulates the growth of cells, providing a basic platform for subsequent biological modification on the substrate by various techniques in bio-MEMS such as lithography, physical vapor deposition and chemical etching. There are sufficient reasons to assume that the bio-inspired materials and properties will be further developed with the help of advanced surface modification techniques. Their application in cardiovascular devices will present a broader concerns and prospects in the near future.

4.2. Construction of an endothelial cell-friendly microenvironment in cardiovascular surface modification

When a synthetic graft is implanted or a vascular stent is expanded, the damage of endothelium is the initiating factor to cause thrombus formation and/or restenosis [116]. During the long healing process, most attention must be paid to the restitution of endothelium. The pith of biomimetic modification is the reconstruction of an endothelial cell-friendly microenvironment. The foreign material should provide a surface for the mediation of ECs from the healthy endothelium to the implanted materials, for the continuous growth and proliferation of ECs with healthy phenotype, expressing and releasing the appropriate

bioactive molecules. This includes sufficient formation of intercellular junctions, expression of antithrombotic molecules and the production of nitric oxide [117]. The most meaningful and inspiring developments in biomimetic surface engineering include two aspects, mimicking endothelial function and mimicking extracellular matrix (ECM) function respectively.

A healthy endothelium normally provides an anticoagulant and anti-proliferative surface, acting as an effective natural protection against thrombosis, lipid uptake and inflammation by releasing signal molecules like nitric oxide, thrombomodulin, prostacyclin, heparin-like molecules, growth factors, tissue plasminogen activator and tissue factor pathway inhibitor [118]. Most methods of preparing anti-coagulation coatings, for example the immobilization of TM or heparin and the construction of NO releasing material, range in this strategy of mimicking endothelial function. Apart from the functional molecules released from ECs, ECM plays a crucial role in supporting the survival of ECs as well. In general, ECM consists of multiple functional proteins and signal molecules. The various components of ECM have been immobilized onto the surface of implants, including various amounts and types of collagens, adhesion molecules, proteoglycans, functional peptides, growth factors, cytokines or chemokines [119]. The remodeling of EC-friendly microenvironment is available by plenty different kinds of methods, which are summarized in Table 1. The results of those reports show that the immobilized molecules contribute to the attachment and adhesion of endothelial cells and enhance the expression of ECs markers, demonstrating that the strategy of constructing EC-friendly microenvironment is effective for endothelialization of cardiovascular implants.

4.3. Self-endothelialization for cardiovascular surface modification

Natural endothelium generally acknowledged the ideal surface for blood contact, but ECs are believed to be end-differentiated cells, which have withdrawn from the cell cycle and are no longer capable of division and expansion [117]. For the past few years, great progress has been obtained by anticoagulant or endothelial-promoted surface modification by either immobilization of active molecules or vascular cell seeding on manufactured cardiovascular materials or prostheses. However, due to

Table 1
Effects of biological modification and categories of immobilized molecules.

Biomolecules		Substrate	Comments	Ref.
Collagens		PLCL	Endothelialization enhanced; mechanical properties suitable for vascular graft	[120]
		NFM		
Proteoglycans		Si, PET, 316L SS	Good hemo-/cyto-compatibility; no difference of neointimal hyperplasia between BMS and Hep/Col stent	[121]
	Fibronectin	Ti	Stable and bioactive coating; blood compatibility and endothelialization improved	[64]
	Tropoelastin	SS	Robust interface suitable for the immobilization of biomolecules, encouraged the attachment of ECs and enhanced their proliferation	[122]
Adhesion molecules/functional peptides	RGD	XG cellulose	XG–RGD increased adhesion, spreading and the metabolism of seeded ECs	[123]
	REDV	SS	Adhesion, spreading, viability and proliferation rate of ECs were enhanced; viability and proliferation of SMCs decreased	[124]
	YIGSR	PU	Enhancement of adhesion, migration, and proliferation of ECs; suppression of platelet adhesion by hydrophilic PEG chains	[125]
Growth factors	VEGF	316L SS	Improvement of hemocompatibility and promotion of re-endothelialization	[60]
		Ti	Increased in EC attachment, viability and proliferation; induced differentiation of hMSCs	[108]
	bFGF	Collagen	Supported adhesion and proliferation of seeded ECs in vitro	[126]
ECM-like		PLCL	Synergistic effects about RGD on migration of ECs and bFGF on expression of ECs	[109]
	SMC-ECM	Ti	SMC–ECM induced fewer platelet adhesion and better growth and viability of ECs in vitro than EC–ECM; EC–ECM led to complete endothelium formation than SMC–ECM in vivo	[127]
	EC-ECM			
	Mixture of Fn/Ln/Fg	Gel scaffold	Pressed ECM-like scaffold promoted the survival condition of EPCs	[128]

Abbreviations in the table: PLCL: poly(L-lactic acid)-co-poly(ϵ -caprolactone); NFM: nanofiber mesh; PET: polyethylene terephthalate; SS: stainless steel. Hep: heparin; Col: collagen; XG: xyloglucan; bFGF: basic fibroblast growth factor; PU: Polyurethaneurea; PEG: polyethylene glycol. hMSCs: human mesenchymal stem cells. SMC-ECM: ECM deposited by SMCs; EC-ECM: ECM deposited by ECs. Fn: fibronectin; Ln: laminin; Fg: fibrinogen; EPC: endothelial progenitor cell.

limited long-term efficiency of biomolecule modified implants, and the time-, labor- and cost- consuming procedure of cell seeding onto implants, only few products found entrance into clinical practice [129]. After the discovery of endothelial progenitor cells (EPCs) in 1997 by Asahara [130], new perspectives of rapid self-endothelialization were put forward and novel strategies of in vivo endothelialization began to be carried out. Currently, induction of EPC homing and capturing on bio-functionalized surfaces represents a wider applied trend for surface modification of cardiovascular implants, especially vascular grafts and stents.

EPCs are a small population of CD34⁺ circulating mononuclear cells that loss the expression of hematopoietic antigens and upregulate expression of endothelial specific antigens during in vitro differentiation, with the capability of colony-forming in vitro and homing at an ischemic injury [131]. These cells exist in bone marrow and peripheral blood in extremely low concentration. EPCs exist in the cardiovascular system as two types, namely early EPC and late EPC [132], suggesting two aspects of exploiting EPCs for rapid self-endothelialization. One is to construct a surface, mobilize and support homing of early EPCs at the injury. The cells then are able to secrete angiogenic cytokines to ensure the survival of the resident ECs and the proliferation of late EPCs. The other aspect is preparing a surface, which is able to capture late EPCs, exploiting key roles in neoangiogenesis and repairing of the vascular injury by virtue of their high proliferation rate [133]. Although the exact signaling pathways involved in EPC homing remains to be tested, some growth factors, cytokines and chemokines such as vascular endothelial growth factor (VEGF), stromal derived factor-1 (SDF-1), nerve growth factors (NGF), granulocyte colony-stimulating factor (G-CSF), hypoxia-inducible factor (HIF), and brain-derived neurotrophic factor are confirmed to participate in the repair of vascular injury and neovascularization by means of molecular biology [134]. Several meaningful attempts have already been conducted, aiming to pilot EPC onto a surface. Meanwhile, a large number of designs are conceived to construct EPCs capturing surface by immobilizing antibodies, peptides, magnetic molecules and aptamers, according to the detail review by Meltem Avci-Adali et al. [135].

For example, Wen Zeng et al. constructed a NGF-bound tissue-engineered blood vessel. The results demonstrated that NGF can markedly increase EPC mobilization and homing to vascular grafts [136]. Jian Yu et al. engineered a SDF/Heparin coating on PLLA/PCL based small-diameter synthetic vascular grafts. The modified grafts have the capability of self-regeneration by recruiting EPCs and SMPs, addressing two issues of cardiovascular implants: endothelialization and remodeling

of the vascular wall [137]. A similar case is that Fn/SDF coating was prepared on clinical available small-caliber vascular grafts, Gelsoft™ and Polymaille®C, improving endothelialization and reducing intimal hyperplasia and thrombosis as well [138]. EPC capture strategy is prone to be applied in vascular stents. Genous R-stent™ is considered as the first clinical device using the EPC capture stent strategy. The early clinical outcomes indicate the safety and efficacy of this stent. Further investigations and more comprehensive studies are being carried out to evaluate the promising applications of Genous R-stent™ and this kind of CD34⁺ antibody stent [139]. Not confine to Genous R-stent™ EPC capture system, stents with similar functions are designed in laboratory by diverse methods. Using the systematic evolution of ligands by exponential enrichment technology, DNA-aptamers with a high affinity to EPCs were identified and isolated by Jan Hoffmann et al. [140]. With the help of phage display technology, Anka N. Veleva et al. [141] isolated 12-mer peptide ligands that bind to human blood outgrowth endothelial cells. These EPC specific molecules, grafted on the polymer disk [140], combined with stents [142], and immobilized on Ti [143], suggested that the rapid adhesion of EPCs to aptamer-coated implants can be useful to promote endothelial wound healing and to prevent increased neo-intimal hyperplasia at some degree. Recently, Joo Myung Lee et al. [144] compared endothelialization and neointimal formation of two EPC capture stents with CD34⁺ antibodies or vascular endothelial-cadherin, respectively coated on BMS. It seemed that VE-cadherin is considered more suitable target molecule than CD34⁺ to be applicable to the manufacturing innovative EPC-capturing stents. Up to date, it's still difficult to evaluate which kind of capture molecule is most helpful for EPCs. Another strategy to achieve luminal unimpeded after surgery is the combination of EPC capture and DES techniques, hopefully being one effective way to minimize the occurrence of any complications [145]. However, plenty of studies in vitro and in vivo require to be done in both applications of stents and grafts. There's every reason to believe that mimicking self-healing system in human, homing stem cell or progenitor cell to the injury and accelerating the repair of damaged endothelium have brought revolutionary prospective for a new generation cardiovascular implants.

5. Concept of time sequence functional cardiovascular implants

Despite the considerable advances in development, selection and modification of cardiovascular implantable materials, there is still a gap between the novel designs of devices and clinic applications. In

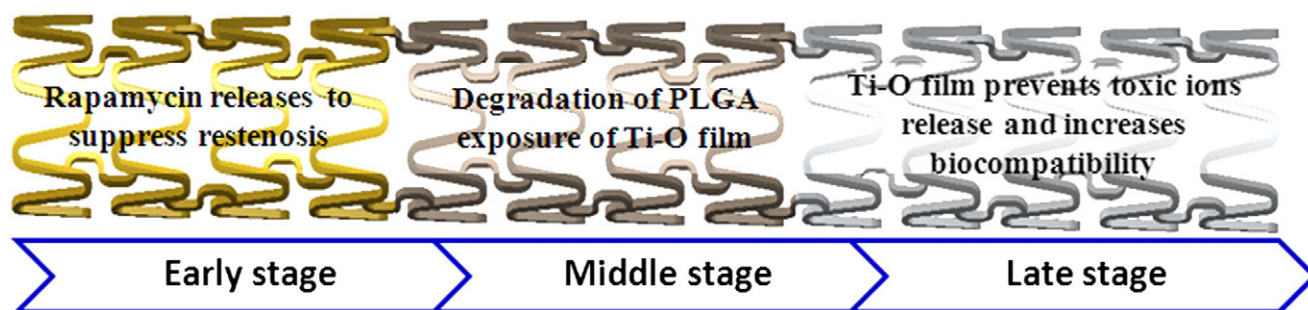


Fig. 6. Schematic of time sequence vascular stent.

9th world biomaterial congress, the author of this paper proposed the concept of “time sequence functional stent”. The same idea could be extended to other cardiovascular devices. In brief, the responses of the biological environment on the cardiovascular device should present the feature of time sequence. It means the ideal device should possess the functions which can match the relative biological responses in each stage. Taking stents which confront the most complex physiological environment as an example, it should always play a positive role in all the biological evolution processes after interventional surgery. In early stage, suppression of restenosis caused by injury due to the stent intervention is required. Then endothelialization is essential in next stage. The late stage should highlight the prevention of toxic ions release from the stent and maintaining stent material/tissue compatibility. The time sequence vascular stent model using Ti–O film in PLGA-rapamycin drug eluting stent has finished its clinical trial. At the acute stage the drug release plays the role to suppress restenosis, and then the drug carrier PLGA is degraded and the Ti–O film surface with improved antithrombotic properties is exposed to blood; Ti–O also supports the endothelialization. In the long-term stage the Ti–O film coating on the stent prevents the release of toxic elements from the stent surface into the surrounding tissue and increased the long-term biocompatibility (Fig. 6). This clinical trial was performed in a multicenter randomized trial in comparison with a commercial stent. 150 patients were adopted for each stent group and totally 251 new stents and 240 reference stents were used. One year clinic results showed that the restenosis rate for the new stent was 1.1% and the late thrombus formation for the new stent was 0, both significantly lower than the control. It can be concluded that this new stent with the novel structure metal stent/Ti–O film/degradable drug eluting coating has displayed the appropriate properties according to the time stage of the vascular response after stent implantation. Another example considering the spatio-temporal delivery, a VEGF gene and paclitaxel co-eluting stent was designed recently. VEGF gene in the outer PLGA layer was released first, playing a major role in rapid repairment of endothelium. Thereafter, paclitaxel as a microtubule-stabilizing agent began to release due to the degradation of outer VEGF–PLGA layer, inhibiting the proliferation of SMCs and inducing their apoptosis. Through sequential release of selected genes and drugs, early endothelium healing and later inhibition of restenosis were both achieved in this stent which matched the conception of time sequence functional stents [90].

In addition, an increasing number of designs in the research field of developing novel cardiovascular devices or materials, tailoring the time sequence delivery of growth factors or drugs are reported in recent years. The complex process, including the migration, differentiation, proliferation or apoptosis of targeted cells and the reconstruction of tissues relies on the presence of specific growth factors or drugs, loading methods and their time-dependent or spatial distribution [146]. Smadar Cohen et al. reported a series of work on the sequential delivery of angiogenic factors. The alginate scaffolds with ability of sequential delivery of VEGF, platelet-derived growth factor-BB and transforming growth factor- β 1 were prepared via their differential affinity binding to alginate-sulfate, leading to the formation of stable

and mature blood vessels after implantation in rat [147]. Applying the same affinity-binding mechanism, an injectable alginate, sequential delivering insulin-like growth factor-1 and hepatocyte growth factor was also achieved to promote myocardial repair [148]. Sequential delivery of vascular endothelial growth factor and sphingosine 1-phosphate for angiogenesis was reported as well [149]. These reports all indicated the focus of spatio-temporal effects on the applications of cardiovascular implants and tissue engineering. Furthermore, the realization of this vision not only demands the biocompatible bioinert coating, but also the assistance of various molecules (e.g. nanoparticles, drugs) immobilized or loaded onto the surface. Predictably, the ideal surface may be constructed by multifunctional groups, for example the dopamine mediated modification. Non-toxic linkers or carriers and co-immobilization of various biomolecules will also achieve a multifunctional surface as we expect.

6. Conclusion

The control of interaction between implanted material and blood or endothelium is crucial for the successful clinical performance of cardiovascular devices. Much endeavor has been made to resolve some of the issues associated with earlier implants. The diverse surface modification strategies and techniques have been applied in order to regulate blood-implant responses. About 20 years ago, anticoagulant surface and antiplatelet agents were emphasized to reduce surface thrombogenicity. Currently the developed heparin coating, direct thrombin inhibitor coating and the recent local release of NO from materials are all in progress and expected to be applied in the next-generation of cardiovascular devices. The two decade development witness the paradigm change in surface modification of such devices from the earliest bio-passivation and further developed bioactive coating to the state-of-the-art strategy of biomimetic endothelialization promoted modification.

However, more basic experiments, animal tests and clinical data need to be carried out and collected to provide theoretical and practical outcomes with the help of investigators, inventors, and biomedical engineering involved in the design, development, and testing of novel generation cardiovascular devices. Surface modification, both traditional methods and advanced biomimetic strategy, will become more interesting and fascinating in development of future cardiovascular devices.

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